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Award Number: W81XWH-07-2-0071

TITLE: Individual Differences in Diabetes Risk: Role of Sleep Disturbances

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REPORT DATE: August 2008

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
01-08-2008	Annual	15 JUL 2007 - 14 JUL 2008

4. TITLE AND SUBTITLE

Individual Differences in Diabetes Risk: Role of Sleep Disturbances

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-07-2-0071

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University Of Chicago
Chicago, IL 60637

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
This first year of support was dedicated to obtain USAMRMC/HRPO/ORP approval of the protocols and to analyze pre-existing data. A review article was submitted.

15. SUBJECT TERMS
Sleep, Diabetes, Slow-Wave activity, Weight Gain

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
U	U	U	UU	44	**19b. TELEPHONE NUMBER** *(include area code)*

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Annual Report for Award Number W81XWH-07-2-0071

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Introduction

Chronic partial sleep loss, due to bedtime restriction, is a hallmark of modern society and highly prevalent in active duty army personnel. During the past few years, evidence from laboratory and epidemiological studies has indicated that decreased sleep duration has an adverse effect on glucose regulation and on the neuroendocrine control of appetite (1-3). Taken together, the findings suggest that chronic partial sleep deprivation may be involved in the current epidemic of obesity and diabetes. Our group has strong evidence for the existence of large individual differences in metabolic as well as cognitive vulnerability to sleep loss. We have recently obtained preliminary data in a small group of young men that suggest that a specific heritable trait of the sleep electroencephalogram (EEG), known as slow-wave activity (SWA), accounts for the majority of individual variability in the adverse effects of sleep loss on diabetes risk.

The objectives are to identify SWA as a predictor of diabetes risk in a subject population with a gender, ethnic and age distribution similar to that of active duty army personnel and to test the hypothesis that individuals with low SWA are at much higher risk to develop diabetes following chronic partial sleep restriction than those with higher SWA. The studies will also explore the potential relationships between individual differences in diabetes risk following sleep loss and individual differences in risk of weight gain and in the magnitude of cognitive deficits.

Body of Report

Overview

In year 1, the approved Statement of Work included the completion of Task 1 and Task 2 as described below and the initiation of Task 3.

Approved Task 1: Testing role of EEG SWA as predictor of individual differences in baseline glucose disposition index (Months 1-6):

Perform spectral analysis of sleep EEG for 56 subjects in whom EEG recordings and glucose and insulin levels during intravenous glucose tolerance testing are presently available

Re-run minimal model analysis of ivGTT results for 56 subjects already tested

Recruit and study 7 additional subjects using currently IRB-approved protocol in order to match gender, age and ethnic distribution of active army personnel

Test the hypothesis that levels of SWA in the sleep EEG are a significant predictor of beta-cell responsiveness and insulin sensitivity after controlling for gender, age, BMI and ethnicity-based diabetes risk.

Define lower and upper thirtiles of slow-wave activity associated, respectively, with putatively high and low diabetes risk during sleep curtailment

Approved Task 2: preparation of clinical study of diabetes risk during sleep curtailment
(Mos. 1-6):

- Submit protocol to and obtain approval from University of Chicago Institutional Review Board and Clinical Research Center
- Import Walter Reed Army Institute of Research battery of neurobehavioral testing and train personnel in its use

Approved Task 3: Completion of clinical study of diabetes risk during sleep curtailment in 32 individuals (Mos. 7-42 – one study per month):

- Recruit and screen 60-70 individuals to enroll 16 individuals with SWA in lower third and 16 individuals with SWA in upper third of distribution with both groups matched for gender distribution
- Complete study in two groups of 16 individuals

Generate individual data analysis and enter in database.

Research accomplishments associated with Task 1

This Task was amended by the United States Army Medical Research and Materiel Command (USAMRMC). Indeed, we were informed that our University of Chicago approved IRB protocol needed to be submitted to HRPO for review and approval prior to the initiation of Task #1 and the enrollment of additional subjects. We were further informed that in order to initiate the analysis of existing de-identified data, the HRPO would also need to review the existing University of Chicago approved IRB protocol and approve the use of the information.

On May 4, 2007, Ms. Johanna Kidwell from USAMRMC, Office of Research Protections (ORP), Human Research Protection Office (HRPO), made the initial contact from HRPO and suggested that, in order to be able to initiate Task #1, we choose one of the following alternatives:

- provide the IRB approval letter, approved protocol and consent form, and all other protocol documentation for the study to HRPO for review and approval prior to enrollment or use of the previously collected data.
- treat this as a new study and prepare a new protocol for the seven additional subjects and the use of the previously collected data.

We chose the first alternative, gathered all the documents and submitted to Ms. Kidwell the original protocol, three subsequent amendments, the corresponding IRB approval letter referencing the changes, the current consent form and the most recent IRB approval letter on June 7, 2007.

On July 13, 2007, Ms. Kidwell gave us an update on the review of our project. She divided the project into two files as follows:

A-14332.1 - for the enrollment of the additional subjects in the existing University of Chicago approved protocol (Task 1).

A-14332.2 - new protocol for Task 2 titled "Individual Differences in Diabetes Risk: Role of Sleep Disturbances."

She requested the enrollment tables and the IRB submission documents, rather than only the approval letter, of the existing University of Chicago approved protocol as only the most recent continuing review report had been sent. These documents were submitted at the end of July 2007.

On September 20, 2007, we received the review of the existing protocol from Ms. Kidwell in a 4-page letter. She noted that the protocol did not include some of the elements required by USAMRMC/ORP/HRPO and requested additional information/revision/clarification in 16 points to be addressed in the protocol. There were also 8 points to address in the consent form and 2 in the advertisement flyer.

After due consideration, a telephone conversation with Ms. Kidwell, and consultation with the University of Chicago IRB, we decided that it would be more efficient to re-write the protocol and consent form as a new protocol than to revise the existing documents.

On October 5, 2007, we submitted a new protocol for task 1 (A-14332.1; 14 pages), consent form (6 pages) and flyer, along with a 14-page letter addressing the comments of the review.

On November 13, 2007, we received the review of the new protocol A-14332.1 from Ms. Kidwell in a 7-page letter. The review included 4 points for revision in the protocol and 7 points in the consent form.

On December 6, 2007, we submitted the revised new protocol A-14332.1 (27 pages), revised consent form and a cover letter explaining the changes.

On January 14, 2008, we received the second review of protocol A-14332.1 from Ms. Kidwell in a 6-page letter requesting only one more revision. Submission of the revised documents that include all HRPO recommended revisions and the

protocol addendum to the University of Chicago IRB after addressing the remaining item was recommended.

On January 16, 2008, we submitted the fully revised A-14332.1 protocol to the University of Chicago IRB.

On February 15, 2008, we received the review of the University of Chicago IRB. The 3-page letter requested revisions to 4 points in the consent form. We submitted a revised version to the University of Chicago IRB on February 22, 2008.

On March 4, 2008, we received IRB approval of protocol A-14332.1, pending certification of Human Subject Protection Training (HSPT) for all research assistants who would be monitoring subjects. All research assistants received training. On March 17, documentation of completion of the HSPT for all RAs was submitted to the IRB. Final approval was received on April 3, 2008

On April 8, 2008, the IRB approved documents were sent to Ms. Kidwell via e-mail. She replied on the same day that all IRB communications relating to this protocol were needed and we provided these documents on April 15, 2008.

On April 21st , we received a review of the new IRB-approved protocol A-14332.1 from Ms. Kidwell. She requested 2 revisions in the protocol and 1 revision in the consent form.

On April 22, 2008, we submitted the revised protocol A-14332.1 to the University of Chicago IRB for approval of the revisions requested by Ms. Kidwell.

On May 1, 2008, we received University of Chicago IRB approval of the revised protocol A-14332.1.

On June 9, we submitted this final version to Ms. Kidwell via email.

On June 9, 2008, we received final approval of this protocol from Ms. ANDREA J. KLINE, MS, CIP, Chief, Research Administrative Support, HRPO, ORP, USAMRMC.

On June 16, we submitted the HRPO-approved protocol to the Internal Scientific Advisory Panel (ISAP) of the University of Chicago Institute for Translational Medicine (CTSA) to obtain approval for the use of the Clinical Resource Center (CRC).

On July 22, 2008, we received a 2-page review from the ISAP including 8 comments to address in the protocol and 1 point to address in the Data and Safety Monitoring Plan.

Our response to the ISAP has been submitted on August 10, 2008. As soon as we receive approval, we will submit the new version of the protocol for approval by HRPO, ORP, USAMRMC and subsequently by the University of Chicago IRB.

Analytical work

We have performed the spectral analysis of the sleep EEG for 44 of the 56 subjects for whom the recordings were readily available. We have manually verified the obtained spectral profiles for accuracy. The automatic artifact removal procedure used has been improved for a better efficiency while working on large data sets. We have also automatized and implemented additional options in the procedure for data extraction according to the sleep cycles. We are currently seeking how to improve the SWA descriptors extracted and computed from the intermediate spectral profiles.

The CD-ROM backup copy of the sleep EEG recordings of the remaining 12 subjects were located and transferred for spectral analysis onto our dedicated computer workstation. Two CD-ROMs could not be read on the CD drive of our pool of computers. We are currently seeking for a solution for the recovery of the corresponding data. The 10 remaining sleep EEG recordings transferred onto the analysis workstation were collected using a different computer acquisition system (Digitrace) and the corresponding computer files consisted of multiple fragments. We have obtained the binary data format specifications of the Digitrace recording files, and are currently implementing a computer program for the concatenation of these fragment files in order to perform their analysis by preserving the temporal continuity of the sleep EEG.

Based on the 44 sleep EEG recordings currently analyzed, the mean SWA in the first 3 hours of sleep was 1573 ± 1115 μV^2 (mean ± SD), and 1008 μV^2 was the upper limit of the lower thirtile while 1625 μV^2 was the lower limit of the upper thirtile. These figures are indicative at this stage as the inclusion of more subjects will clearly modify the cut off points for low and high SWA, respectively. The distribution of SWA from the 44 subjects conforms with expectations regarding the impact of sex, with women having higher SWA than men.

It is clear that if the cut offs points for low and high SWA, respectively, were derived from a larger data base of recordings obtained in subjects with a sex, age, ethnic and BMI distribution similar to that of active duty Army personnel, these cut off points would have greater precision. While working to obtain final approval of our protocols from USAMRMC, we have continually updated our data base of recordings accumulated in our laboratory since the submission of our proposal to the PRMPR in May 2006. These data have been obtained as a result of baseline testing of volunteers entering IRB-approved NIH-funded studies where sleep duration or quality was subsequently manipulated. In each individual, baseline polysomnography was performed after at least 2

nights of normal bedtimes (8-9 hours) and a frequently sampled ivGTT was performed on the following day.

Tables 1 and 2 show the gender, age and ethnic distribution of subjects currently in our data base. BMI was <27 kg/m^2 in women and <28 kg/m^2 in men, consistent with recommendations for active duty Army personnel. The data base has more than tripled in size (to 171 from 56) since our original submission. It can be seen that the gender and ethnic distributions are similar to that of active duty Army personnel but that very young individuals are still underrepresented in our sample. In particular, the data base includes only 6 subjects under 20 years of age. Thus, the planned recruitment of additional subjects in the 17-20 yr age category (6 men and 1 woman in order to preserve the gender distribution) remains necessary. Nonetheless, this enlarged data base will greatly enhance the accuracy of the definition of the cut off points of low and high SWA.

TABLE 1	*The 2008 University of Chicago Database*		Active Duty Army Demographics (FY04)
MEN			
White	87	71.3 %	63.2 %
Black	24	19.7 %	19.9 %
Hispanic	7	5.7 %	10.2 %
Other	4	3.3 %	6.7 %
Total	122	100 %	100 %
WOMEN			
White	26	53.1 %	41.7 %
Black	14	28.6 %	38.8 %
Hispanic	5	10.2 %	11.1 %
Other	4	8.2 %	8.4 %
Total	49	100 %	100 %

TABLE 2	*The 2008 University of Chicago Database*		Active Duty Army Demographics (FY04)
GENDER			
Men	122	71.3 %	85.3 %
Women	49	28.7 %	14.7 %
Total	171	100 %	100 %
AGE			
17- 20 years	15	8.8 %	14.2 %
21-24 years	65	38.0 %	26.7 %
25-29 years	42	24.6 %	21.1 %
30-39 years	31	18.1 %	27.7 %
$\geq$ 40 years	18	10.5 %	10.4 %
After proposed recruitment of 6 men and 1 woman in 17-20 years age category			

GENDER			
Men	128	71.9 %	85.3 %
Women	50	28.1 %	14.7 %
Total	178	100 %	100 %
AGE			
17- 20 years	22	12.9 %	14.2 %
21-24 years	65	36.5 %	26.7 %
25-29 years	42	23.6 %	21.1 %
30-39 years	31	17.4 %	27.7 %
$\geq$ 40 years	18	10.1 %	10.4 %

Minimal model analysis of ivGTT for the 44 subjects for whom spectral analysis has been completed has been performed and the results are being verified for accuracy.

***Research accomplishments associated with* Task 2**

Submit protocol to and obtain approval from University of Chicago Institutional Review Board and Clinical Research Center

Although this task was supposed to be initiated after the beginning of funding, we were advised to anticipate the award date and prepare the necessary documents. We thus expanded human resources prior to funding.

On April 11, 2007, we submitted the protocol (25 pages) and consent form (13 pages) to Ms. Amber Stanley of Azimuth, Inc. She indicated on April 12, 2007, that the documents had been submitted to ORP.

On May 4, 2007, Ms. Johanna Kidwell acknowledged receipt of these documents.

On July 13, 2007, Ms. Kidwell gave us an update on the review of our project. She divided the project into two files as follows:

A-14332.1 - for the enrollment of the additional subjects in the existing University of Chicago approved protocol (Task 1).

A-14332.2 - new protocol for Task 2 titled "Individual Differences in Diabetes Risk: Role of Sleep Disturbances."

On August 14, 2007, we received the initial review of A-14332.2 from Ms. Kidwell in a 13-page document requesting 24 revisions in the protocol and 12 revisions in the consent form.

On September 3, 2007, we submitted a revised version of protocol A-14332.2 (version 2) and related documents (consent, DSMP, CV of the medical monitor) along with a cover letter.

On October 24, 2007, we received a second review of A-14332.2 from Ms. Kidwell in a 9-page letter requesting 2 revisions in the protocol and 3 in the consent form.

On November 7, 2007, we submitted a second revision of protocol A-14332.2 and related documents to Ms. Kidwell (version 3), along with a cover letter.

On November 20, 2007, we received a third review of A-14332.2 from Ms. Kidwell in a 9-page letter requesting one more revision in the protocol and one more in the consent form.

On November 30, 2007 the most recent requested revisions for 14332.2 were submitted.

On December 17, 2007, a final request from Ms. Kidwell for minor changes to the protocol (A 14332.2) was received with approval pending receipt of the revised documents.

On January 14, 2008, Ms. Kidwell recommended submission of the revised documents that include all HRPO recommended revisions and the protocol addendum to the University of Chicago IRB.

On January 14, 2008, the protocol for A 14332.2 was submitted to the University of Chicago IRB.

On February 5, 2008, protocol A 14332.2 was reviewed at the regular Committee meeting of the University of Chicago IRB. The protocol received pending-conditional approval. The 2-page letter mentioned 4 changes to the consent forms as well as revisions to the recruitment ads and requested that all research assistants complete the Human Subjects Protection Training before full approval could be granted.

We submitted a revised revision to the University of Chicago IRB on February 22, 2008.

On March 4, 2008, we received IRB approval of protocol A-14332.2, pending certification of Human Subject Protection Training (HSPT) for all research assistants who would be monitoring subjects. All research assistants received training. On March 17, documentation of completion of the HSPT for all RAs was submitted to the IRB. Final approval was received on April 3, 2008.

On April 8, 2008, the IRB approved documents were sent to Ms. Kidwell via e-mail. She replied on the same day that all IRB communications relating to this protocol were needed and we provided these documents on April 15, 2008.

On April 21st , 2008, we received a review of the new IRB-approved protocol A-14332.2 from Ms. Kidwell. She requested 2 revisions in the protocol and 1 revision in the consent form.

On April 22, 2008, we submitted the revised protocol A-14332.2 to the University of Chicago IRB for approval of the revisions requested by Ms. Kidwell.

On May 1, 2008, we received University of Chicago IRB approval of the revised protocol A-14332.2.

On June 9, 2008, we submitted this final version to Ms. Kidwell via email.

On June 9, 2008, we received final approval of this protocol from Ms. ANDREA J. KLINE, MS, CIP, Chief, Research Administrative Support, HRPO, ORP, USAMRMC.

On June 16, 2008, we submitted the HRPO-approved protocol to the Internal Scientific Advisory Panel (ISAP) of the University of Chicago Institute for Translational Medicine (CTSA) to obtain approval for the use of the Clinical Resource Center (CRC).

On July 22, 2008, we received a 2-page review from the ISAP including 10 comments to address in the protocol and 2 points to address in the Data and Safety Monitoring Plan.

Our response to the ISAP has been submitted on August 10, 2008. As soon as we receive approval, we will submit the new version of the protocol for approval by HRPO, ORP, USAMRMC and subsequently by the University of Chicago IRB.

Import Walter Reed Army Institute of Research battery of neurobehavioral testing and train personnel in its use

We originally proposed to include a subcontract to WRAIR with Dr. T. Balkin as principal investigator. The object of the subcontract was to analyze and interpret data collected at the University of Chicago in subjects to whom we would administer the WRAIR battery of tests of neurocognitive performance. The USAMRAA award specialist deleted this subcontract from the award. We were still hoping to have a collaborative arrangement involving sharing de-identified data with Dr. Balkin and his senior collaborator Tracy Rupp to receive input regarding analysis and interpretation. This limited collaboration was deemed to

necessitate a full review of our experimental protocol by the WRAIR Division of Human Subjects Protection. Ms. Ball provided an expert full review of the protocol. The protocol had however been separately reviewed by Ms. Johanna Kidwell of the Human Research Protection Office of USAMRMC and had been already through two rounds of revisions. The version of the protocol provided to Ms. Ball was very close to full approval by USAMRMC and we were concerned that introducing any revisions requested by the WRAIR Division of Human Subjects Protection would need to be approved by USAMRMC and result in further rounds of reviews and revisions. In order to be able to initiate this important research, in agreement with Dr. Balkin, we have canceled our plans for collaboration. We have contacted the provider of the Automated Neuropsychological Assessment Metrics (ANAM) software, a commercial version of the Walter Reed Army Institute for Research battery of neurobehavioral testing, and have submitted a request for ordering. After being selected eligible to the End User License Agreement, we have been provided with a CD-ROM of the software. The ANAM software has been installed on a computer and is under current assessment by the investigator.

We will analyze the data from this ANAM battery ourselves and we will not share the data with WRAIR. We will present the summary data at national meetings and hope at that time to receive comments from Dr. Balkin regarding interpretation and relevance to military operations.

Key Research Accomplishments

We believe that we are close to obtain full approval of our protocols by USAMRMC and to be in a position to initiate experimental work. The process has been extraordinarily lengthy and labor-intensive.

The effort to increase our data base will be valuable to the entire project.

While progressing through the regulatory process, we have prepared two reviews on sleep loss and the risk of obesity and diabetes and both are currently in press (see appendices).

Reportable Outcomes

Two review articles have been prepared and are currently in press. Both acknowledged support from this award. They are appended to this report.

Conclusions

We eagerly wait for final approval of the protocols. Work performed in the interim will be valuable to the final outcome of the project. The preparation of review articles has indicated that the body of evidence supporting the hypotheses to be tested in the present project has clearly increased.

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Appendices.

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Sleep and the Epidemic of Obesity in Children and Adults

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Running title: Sleep and Obesity

Word count: 2,895

Abstract

Sleep is an important modulator of neuroendocrine function and glucose metabolism in children as well as in adults. In recent years, sleep curtailment has become a hallmark of modern society with both children and adults having shorter bedtimes than a few decades ago. This trend for shorter sleep duration has developed over the same time period as the dramatic increase in the prevalence of obesity. There is rapidly accumulating evidence from both laboratory studies and epidemiologic studies to indicate that chronic partial sleep loss may increase the risk of obesity and weight gain. The present article reviews laboratory evidence indicating that sleep curtailment in young adults results in a constellation of metabolic and endocrine alterations, including decreased glucose tolerance, decreased insulin sensitivity, elevated sympatho-vagal balance, increased evening concentrations of cortisol, increased levels of ghrelin levels, decreased levels of leptin and increased hunger and appetite. We also review cross-sectional epidemiologic studies associating short sleep with increased body mass index and prospective epidemiologic studies that have shown an increased risk of weight gain and obesity in children and young adults who are short sleepers. Altogether, the evidence points to a possible role of decreased sleep duration in the current epidemic of obesity.

The epidemic of obesity and sleep curtailment in adults and in children

The prevalence of obesity is increasing worldwide, particularly in the US (1). In 2004, more than one third of American adults were overweight or obese (2). Rates of overweight and obesity have also increased in all industrialized countries, although prevalence is still lower than in the US. Figure 1 shows the prevalence of obesity (body mass index [BMI] > 30 kg/m^2) in selected European countries in 1998 and 2001 (3). Prevalence rates range from less than 8% to nearly 14%, depending on country and sex, and remarkably the proportion of obese individuals in the general adult population increased over the 3-year follow up period in all but one country. The epidemic of obesity has not spared children. Figure 2 shows the increase in prevalence of overweight among U.S. children ages 2-5 years, ages 6-11 years and ages 12-19 years from the early seventies to 2003-2004 (4). In each age group, the prevalence of overweight approximately tripled over these three decades.

The causes of this epidemic are not fully explained by changes in traditional lifestyle factors such as diet (increases in food intake, food portions and snacking) and decreases in physical activity. It has been recently proposed that shorter habitual sleep times may also be on the causal pathways (5). Indeed, one behavior that seems to have developed during the past few decades and has become highly prevalent, particularly among Americans, is sleep curtailment. In 1960, a survey study conducted by the American Cancer Society found modal sleep duration to be 8.0 to 8.9 hours (6), while in 1995 the modal category of the survey conducted by the National Sleep Foundation poll had dropped to 7 hours (7). Today, more than 30% of adult men and women between the ages of 30 and 64 years report sleeping less than 6 hours per night (8).

Very few studies have assessed usual sleep duration using objective measures, rather than self-report. An ancillary study to the Coronary Artery Risk Development in Young Adults

(CARDIA) Study, a prospective multi-center cohort study of the evolution of cardiovascular risk factors begun in 1985, measured sleep in participants aged 38 to 50 years (9). In each participant, sleep duration was measured by wrist actigraphy and sleep logs for 3 consecutive days on 2 occasions spaced approximately 1 year apart. Actigraphy involves instruments sensitive to movement, typically worn on the wrist, to record activity continuously over time. Validated software programs determine sleep duration from this activity data. In the CARDIA sleep study, mean (±standard deviation) for sleep duration was 6.1 (1.2) hours, and varied between the race-sex groups from 6.7 (0.9) hours in white women to 5.1 (1.3) hours in African-American men (9). Insufficient sleep appears also highly prevalent in U.S. children. Laboratory studies have shown that "sleep need," defined as the amount of sleep achieved when given 10 hours of nocturnal bedtime, does not change substantially across adolescence (10 to 17 years) and is about 9 hours (10). Contrasting with this physiologic sleep need of 9 hours, are self-reported sleep durations collected in a sample representative of the U.S. more than a 2006 survey conducted by the U.S. National Sleep Foundation (11). As shown in Figure 3, mean sleep duration was under 9 hours in all age groups and decreased steadily from 8.4 hours at ages 11-12 years to only 6.9 hours at ages 17-18 years. The study further showed that the decrease in sleep duration was mostly due to later bedtimes, rather than earlier wake up times, and that the respondents were aware of having insufficient sleep.

The decrease in average sleep duration in the U.S. has occurred over the past three to four decades, simultaneously with the increase in the prevalence of obesity. In recent years, data from both laboratory and epidemiologic studies have accumulated to support the hypothesis that sleep curtailment may have contributed to the increased prevalence of overweight and obesity. Sleep curtailment may affect energy balance and result in weight gain via three distinct

pathways: upregulation of appetite, more time to eat and/or a decrease in energy expenditure. Significant weight gain may in turn result in insulin resistance, a condition that may promote further adiposity. Additionally, up to 20% of overweight and obese individuals suffer from sleep-disordered breathing (SDB), an independent risk factor for insulin resistance (12, 13). The present article will, however, only focus on sleep loss resulting from behavioral sleep restriction rather than from the presence of a sleep disorder.

Laboratory studies linking sleep loss and upregulation of appetite

Early studies reported increased food intake in human subjects and in laboratory rodents submitted to total sleep deprivation (14, 15). The first detailed laboratory study that examined the effects of recurrent partial sleep deprivation on hormonal and metabolic variables involved in appetite regulation included healthy young men who were subjected to 6 nights of 4 hours in bed ("sleep debt") followed by 7 nights of 12 hours in bed ("sleep recovery") (16). The subjects also underwent a baseline study with the recommended 8-hour bedtimes. They ate identical carbohydrate-rich meals and were at continuous bed rest on the last two days of each bedtime condition. At the end of each condition, the subjects underwent an intravenous glucose tolerance test (ivGTT) followed by a 24-hour period of blood sampling at 10-30 minutes intervals to assess glucose and hormonal profiles.

The upper panels of Figure 4 shows the mean profiles of plasma leptin observed under the three conditions (17). Leptin is a peripheral endocrine signal released by the adipocytes that conveys information regarding energy balance to the brain. Leptin is a satiety factor: high leptin levels inhibit and low leptin levels stimulate hunger and food intake. The data shown in Figure 4 demonstrate that leptin levels are remarkably sensitive to sleep duration, with a "dose-response" relationship between sleep duration and leptin consistent with increased hunger when sleep is

curtailed. Indeed, on average, mean leptin levels were 19% lower when the subjects had 4 hours in bed than when they were presumably fully rested, after 6 days with 12 hours in bed. The normal nocturnal acrophase of peripheral leptin concentrations was 2 hours earlier and 26% lower and the amplitude of the diurnal variation was 20% lower during sleep restriction as compared to the fully rested condition (17). Remarkably, these changes occurred despite identical caloric intake. Differences in energy expenditure between the two bedtime conditions were minimal because the subjects were at bed rest. In ongoing studies, our group has preliminary evidence indicating that the extension of the waking period in humans studied under comfortable sedentary conditions is not associated with an increase in energy requirement as assessed by the doubly labeled water method. The difference in maximal leptin levels between the state of sleep debt and the fully rested state was somewhat larger than the decrease reported in a separate study in young adults submitted to three days of dietary intake restricted to 70% of energy requirements (a caloric deficit of approximately 900 Kcal per day) (18). Thus, in the state of sleep debt, leptin levels were inaccurately signaling a state of substantial caloric deficit. Unfortunately, subjective feelings of hunger and appetite were not assessed in this first "sleep debt study".

It is well known that glucocorticoids increase food intake and, in the same sleep debt study, alterations in the 24-hour profile of circulating cortisol levels were also observed (shown in the middle panels of Figure 4). While 24-hour mean levels were similar under the three bedtime conditions, sleep duration affected cortisol levels in the late afternoon and evening (shaded areas) with a graded inverse relationship between sleep duration and cortisol levels (17). The nadir of cortisol concentrations occurred approximately one and a half hours later when subjects had a 4-hour bedtimes as compared to when they had 12-hour bedtimes. Leptin and

cortisol levels varied in a mirror image throughout the 24-hour cycle when the subjects were fully rested, and maximum leptin levels were essentially aligned with minimum cortisol concentrations. This inverse relationship was disrupted following sleep restriction. Leptin levels stopped rising in the early evening, when cortisol concentrations were still declining, and this curtailment of the leptin elevation was quantitatively associated with the concomitant elevation of evening cortisol levels. The study further revealed that alterations of the 24-hour leptin profile resulting from sleep restriction in healthy individuals studied under conditions of stable caloric intake and activity levels were associated with an increase in cardiac sympatho-vagal balance (17).

Another finding of this first laboratory study of metabolic alterations resulting from the experimental build up of a sleep debt was a nearly 40% decrease in glucose tolerance to levels consistent with a state of impaired glucose tolerance (16). Reduced glucose tolerance to intravenous glucose tolerance testing was associated with a marked reduction in acute insulin response to glucose and a trend for reduced insulin sensitivity. The combination of these two defects resulted in a marked decrease in the so-called disposition index (DI), a validated marker of diabetes risk where low DI values indicate an elevated risk of type 2 diabetes. The lower panels of Figure 4 show the profiles of homeostasis model assessment (HOMA) values (glucose concentration (mmol/L) * insulin concentration (mIU/L) divided by 22.5) calculated for each time point. Fasting levels of HOMA are a validated measure of insulin sensitivity but HOMA values during meal ingestion were used here as an integrated measure of the glucose and insulin responses to the three identical carbohydrate-rich meals ingested during the study. The post-breakfast HOMA (shown as a shaded area) was significantly elevated (+56 %) when the subjects were in a state of sleep debt, as compared to fully rested, and the response was intermediate

when the subjects had 8 hours in bed. Subsequent studies of more extended periods of less rigorous sleep restriction (e.g. 8 nights with 5 hours in bed) have revealed a consistent decline in insulin sensitivity without appropriate compensation by beta-cell responsiveness, and thus an increase in diabetes risk. In summary, reduced insulin sensitivity is another possible mechanism by which a state of sleep debt might increase the risk of weight gain and obesity.

A subsequent laboratory study, which used a randomized cross-over design to compare the impact of restricted versus extended sleep, observed consistent effects of sleep restriction on appetite regulation (19). This study involved 2 days of 4-hour bedtimes and 2 days of 10-hour bedtimes in subjects receiving a constant glucose infusion as their only source of caloric intake. Daytime levels of leptin, ghrelin, hunger and appetite were measured at frequent intervals after the 2nd night of sleep restriction or extension (19). Ghrelin is a hunger hormone primarily secreted by the stomach that appears to act independently of leptin. Table 1 summarizes the changes in leptin, ghrelin, hunger and appetite when sleep was restricted as compared to extended (19). Importantly, the change in the ratio of ghrelin-to-leptin between the two conditions was strongly correlated to the change in hunger ratings, suggesting that the changes observed in these appetite hormones was partially responsible for the increase in appetite and hunger. These observed changes would suggest that these subjects, if allowed unlimited amounts of food, would have increased their food intake. After sleep restriction, the increase in appetite was particularly strong for nutrients with a high carbohydrate content (Table 1) as if the sleep-deprived brain craved its primary fuel, glucose.

Two population-based studies, The Wisconsin Sleep Cohort Study (20) and the "Quebec en Forme" study from Canada (21) also observed an association between short sleep duration and changes in leptin and/or ghrelin consistent with an upregulation of appetite. Both studies

included a large number of subjects, measured hormonal levels on a single sample and controlled for the degree of adiposity. Remarkably, as illustrated in Figure 5, the findings from these two population studies were qualitatively and quantitatively in agreement with the findings of the laboratory study.

The notion of "leptin resistance" has been introduced to explain the paradoxical observation that most obese individuals have high, rather, than low plasma leptin levels, despite their ample energy stores. While a number of putative mechanisms have been proposed to underlie leptin resistance, one suggestion that may be particularly relevant to studies of sleep loss is the hypothesis that leptin binds to circulating levels of C-reactive protein (CRP), an inflammatory marker that is elevated in obesity (22). Higher CRP levels would result in a decrease in unbound, free, leptin with a reduction in its central actions. Several studies of acute total sleep deprivation as well as recurrent partial sleep deprivation in healthy lean adults have reported an elevation of CRP with sleep loss (23) and ongoing studies from our laboratory confirm these findings. The combination of reduced leptin levels with increased CRP concentrations in sleep-deprived subjects may amplify the effects of the leptin reduction alone.

In summary, the findings from laboratory studies indicate that reduced sleep duration may increase the risk of weight gain and obesity by upregulating appetite via a decrease in leptin, an increase in ghrelin and a reduction in insulin sensitivity. It is likely that the orexin system is pivotal in theses interaction between sleeping and feeding. Orexins (also called hypocretins) are two distinct peptides (orexin A and B) that were discovered in 1998 and are synthesized mainly by neurons in the lateral hypothalamus. These neurons play a central role in the maintenance of arousal. Orexins (as suggested by their name) also increase feeding (24, 25), particularly at a time when normal food intake is low. Feeding requires the maintenance of wakefulness and the

orexin system appears to be the crucial link in this vital interaction between feeding and arousal. Orexin neurons are active during the waking phase, in synchrony with neuronal activity in other arousal centers, and inactive during slow-wave sleep. Orexins activate all the components of the ascending arousal system, and orexin neurons also project diffusely to the entire cerebral cortex.(26) Consistent with the fact that sympathetic nervous activity is higher during waking than during sleeping, orexin activity is associated with increased sympathetic tone and excitatory effects of the orexin peptides have been observed for neurons of the nucleus tractus solitaries and for neurons of the hypothalamic paraventricular nucleus.(27) In animal models, sleep deprivation upregulates central orexin activity.(28, 29) Increased sympathetic nervous activity associated with sleep deprivation is a likely mediator of several of the peripheral effects of sleep loss, including the reduction in leptin levels and insulin sensitivity and the failure of beta-cells to adequately compensate for the decrease in insulin sensitivity.

Epidemiologic studies linking short sleep loss and increased risk of obesity

A rapidly growing body of epidemiologic evidence supports the findings from the epidemiologic studies. Table 2 summarizes the studies to date (April 10, 2008). Taken together, the studies have involved thousands of subjects, both adults and children of all ages. They have originated from multiple industrialized countries and have involved diverse populations in terms of sex, age and BMI distribution. Patel and Hu (30) have recently provided a careful review of the evidence and pointed out that the impact of short sleep on obesity risk appears greater in children than in adults, and greater in young adulthood than in midlife or late life. This systematic review identified six cross-sectional studies with negative findings or with positive findings in only one sex group (out of a total of 20 cross-sectional studies in adults included in

this analysis). One of the studies characterized as negative (9) focused on race-sex differences in sleep duration and quality objectively assessed by wrist actigraphy in the CARDIA Chicago cohort. Indeed, in this analysis, BMI was not a significant mediator of race-sex differences in sleep. For the purpose of the present article, we identified five more cross-sectional studies in adults not included in the Patel and Hu review (31-35) and therefore, to date, there have only been four studies (36-38, 33) out of a total of 25 that have not observed a cross-sectional association between short sleep and the risk of overweight/obesity in adults of either sex. Of note, two of these studies included only participants over 50 years of age (36, 33).

Conclusions

Findings from laboratory studies in young adults and epidemiologic studies in both children and adults converge to suggest that partial chronic sleep restriction, an increasingly prevalent behavior in modern society, may increase the risk of weight gain and play a role in the current epidemic of obesity. The present challenge for this emerging field of enquiry will be to translate the findings from short term well controlled laboratory studies in small numbers of subjects to the lifetime trajectory of weight gain observed in large populations. Thus, laboratory studies will need to be complemented by studies conducted in real life conditions over longer periods of follow up with an accurate monitoring of sleep duration and quality and energy balance. The observation that the impact of sleep duration and quality on the risk of obesity may be greater in children than in adults suggests that efforts to educate the public regarding the potential deleterious effects of sleep curtailment on long term health and well being should start in early life and involve parents, educators and health care providers.

Acknowledgements

Some of the research described in this article was supported by U.S. National Institute of Health grants PO1 AG-11412, RO1 HL-075079, P60 DK-20595, R01 DK0716960 and M01 RR000055 and by ES Department of Defense award W81XWH-07-2-0071.

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Figure Legends

Figure 1. Prevalence of obesity (BMI> 30 kg/m^2) in nine European countries in 1998 and 2001 (adapted from reference 3).

Figure 2. Prevalence of overweight (defined as above the 95^{th} percentile for age and sex) among U.S. children ages 2-5 years, 6-11 years and ages 12-19 years in 1971-1972, 1976-1980, 1988-1994, 1999-2000, 2001-2002 and 2003-2004 (adapted from reference 4).

Figure 3. Self-reported sleep duration (hours) by age for U.S. children aged 11 years to 18 years. (11).

Figure 4. Mean (±SEM) 24-h leptin, cortisol, and HOMA profiles with 4-h, 8-h, and 12-h bedtimes. Note that the relative synchronization of the leptin and cortisol profiles in the study with 8-h bedtimes was intermediate between that observed with 4-h bedtimes and that observed with 12-h bedtimes. Similarly, the HOMA response to breakfast gradually increased from the 12-h bedtime condition to the 4-h bedtime condition, with an intermediate response during the 8-h bedtime condition. *Black bars*, Sleep periods. (Copied with permission from reference 17).

Figure 5. Percent difference in levels of leptin and ghrelin comparing short sleep to longer sleep conditions from three different studies (19-21).

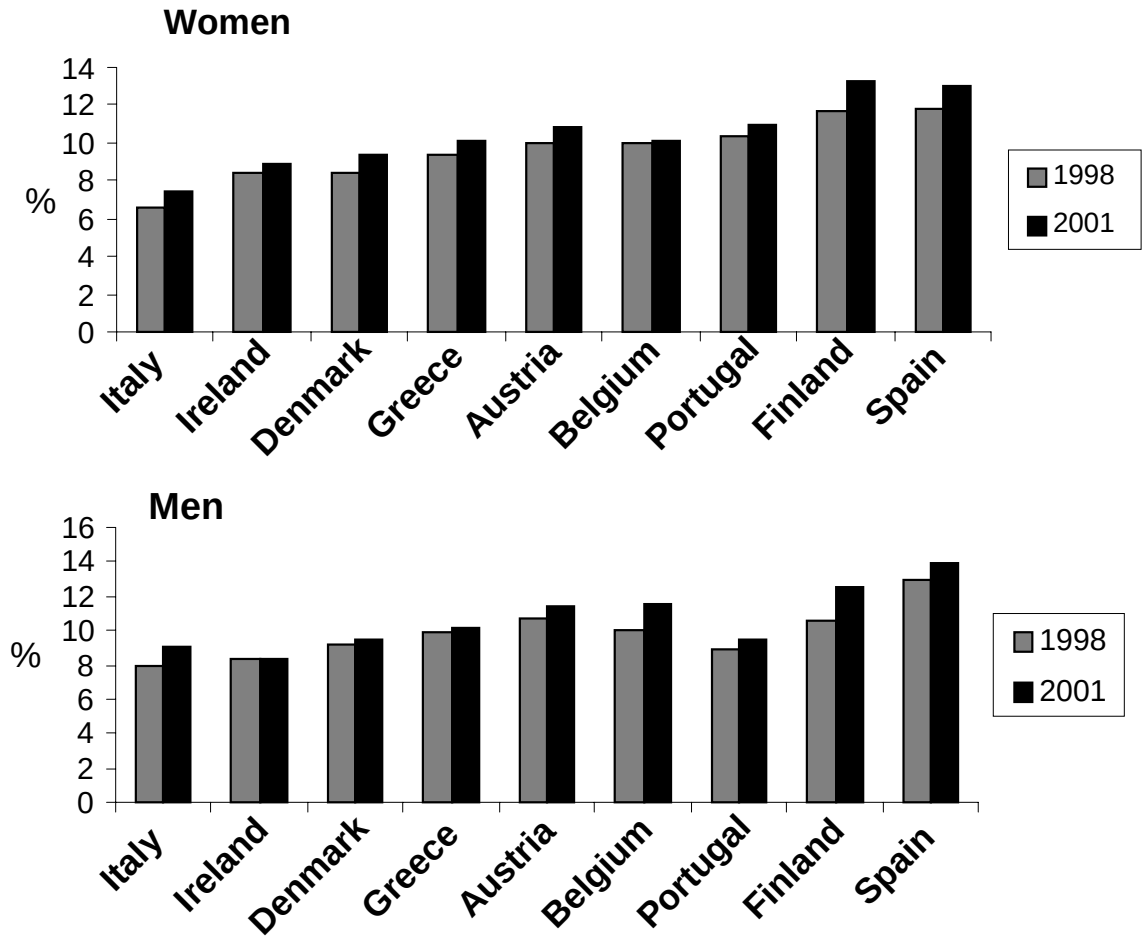
Table 1: Summary of effects of 4-hour and 10-hour bedtimes Hunger and appetite were measured on visual analogue scales.

MEAN (± SEM) LEVELS	**AFTER 2 DAYS of 4-h BEDTIME**	**AFTER 2 DAYS of 10-h BEDTIME**	**CHANGE (%)**	**P**
Plasma Leptin (ng/ml)	2.1 ± 0.4	2.6 ± 0.5	-18%	0.04
Plasma Ghrelin (ng/ml)	3.3 ± 0.2	2.6 ± 0.2	+28%	<0.04
Ghrelin/Leptin ratio	2.3 ± 0.4	1.6 ± 0.3	+71%	<0.07
Hunger (0–10 cm)	7.2 ± 0.4	6.0 ± 0.5	+24%	<0.01
Global appetite (0–70 cm)	47.7 ± 3.4	39.7 ± 3.0	+23%	=0.01
Appetite for high carbohydrate food (0–30 cm)	20.6 ± 1.4	16.3 ± 1.3	+32%	<0.02
Appetite for other food types (0–40 cm)	27.1 ± 2.2	23.4 ± 1.8	+18%	<0.2

Table 2: Number of published epidemiologic studies on the relationship between sleep duration and body mass index (BMI) or prevalence or incidence of overweight/obesity. References for each study can be found in the 2008 review by Patel and Hu (30) with the following additions that were not included in the Patel and Hu review. Cross-sectional studies in children : Nixon, Sleep 2008 (39) and Yu, Sleep 2007 (40). Cross-sectional studies in adults: Stranges, AJE 2008 (31); Lopez-Garcia AJCN 2008 (32), Littman et al 2006 (negative) (33), Rontoyanni 2007 (34), Bjorvatn 2007 (35). Prospective studies: Chaput et al, 2008 (41), Taveras et al, 2008 (42).

	NUMBER OF STUDIES IN CHILDREN		**NUMBER OF STUDIES IN ADULTS**		**TOTAL NUMBER OF STUDIES**	
	Positive Findings	**Total Number of Studies**	**Positive Findings**	**Total Number of Studies**	**Positive Findings**	**Total Number of Studies**
CROSS SECTIONAL **STUDIES**	**13**	**13**	**21**	**25**	**34**	**38**
PROSPECTIVE STUDIES	**3**	**3**	**4**	**4**	**7**	**7**
ALL STUDIES	**16**	**16**	**25**	**29**	**41**	**45**

Figure 1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Finland
Spain
1998
2001
Men
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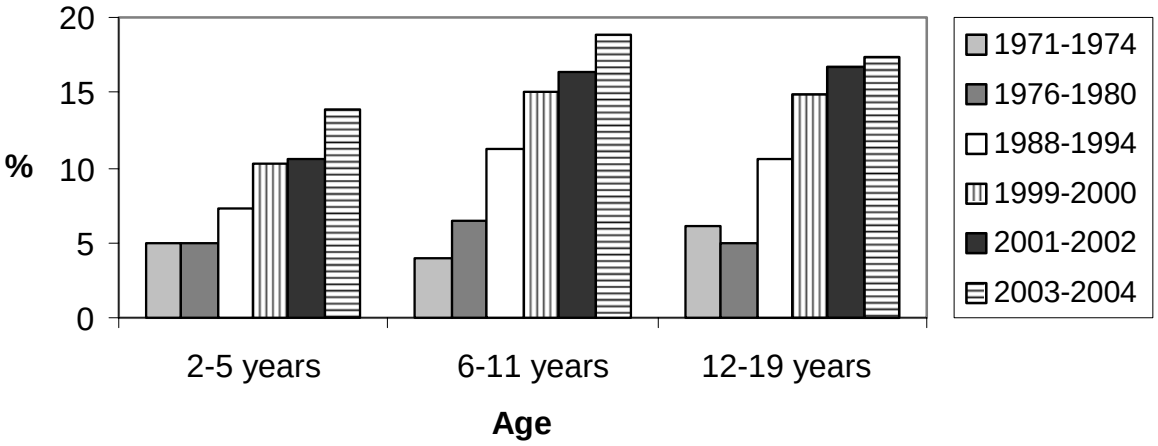
Belgium
Portugal
Finland
Spain
1998
2001

Figure 2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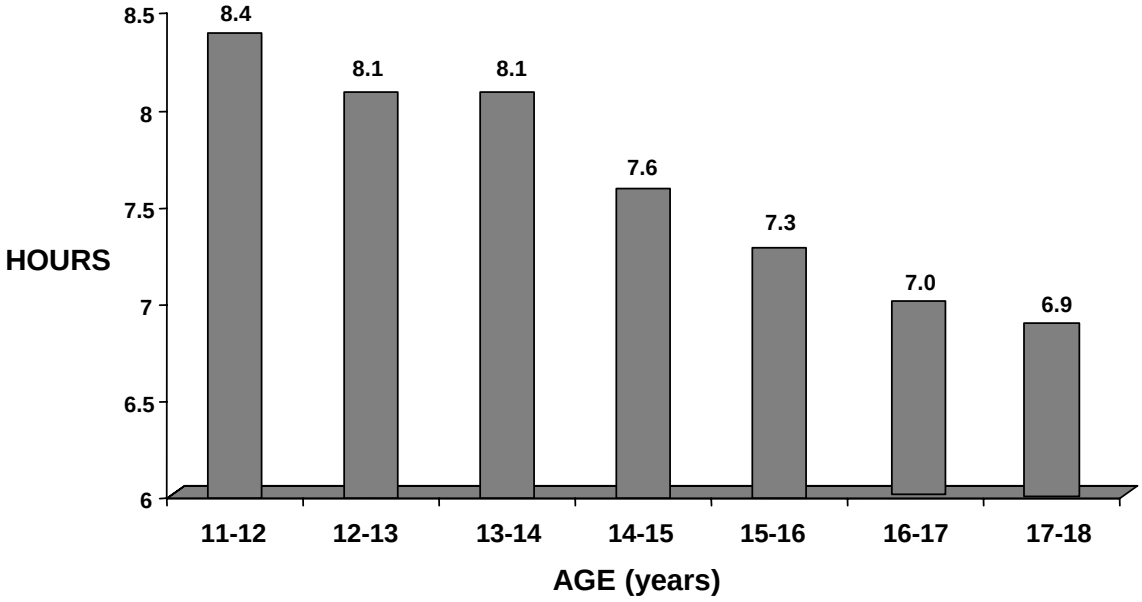
2003-2004

Figure 3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AGE (years)

Figure 4

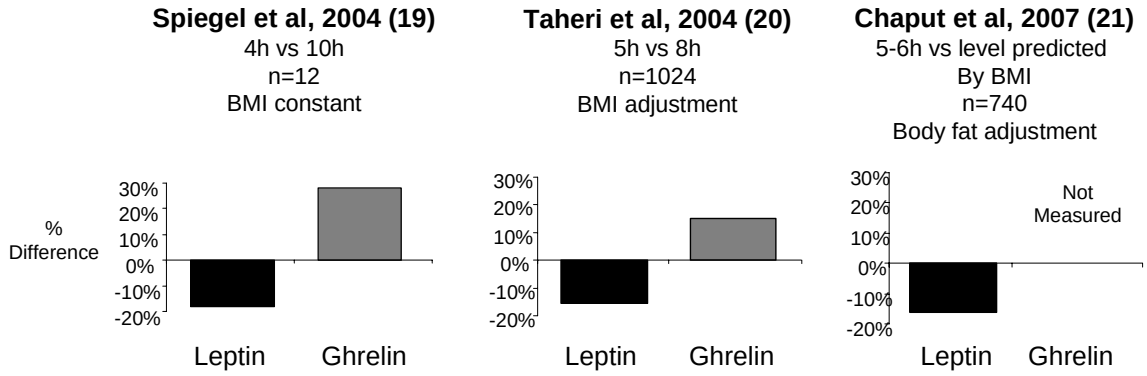
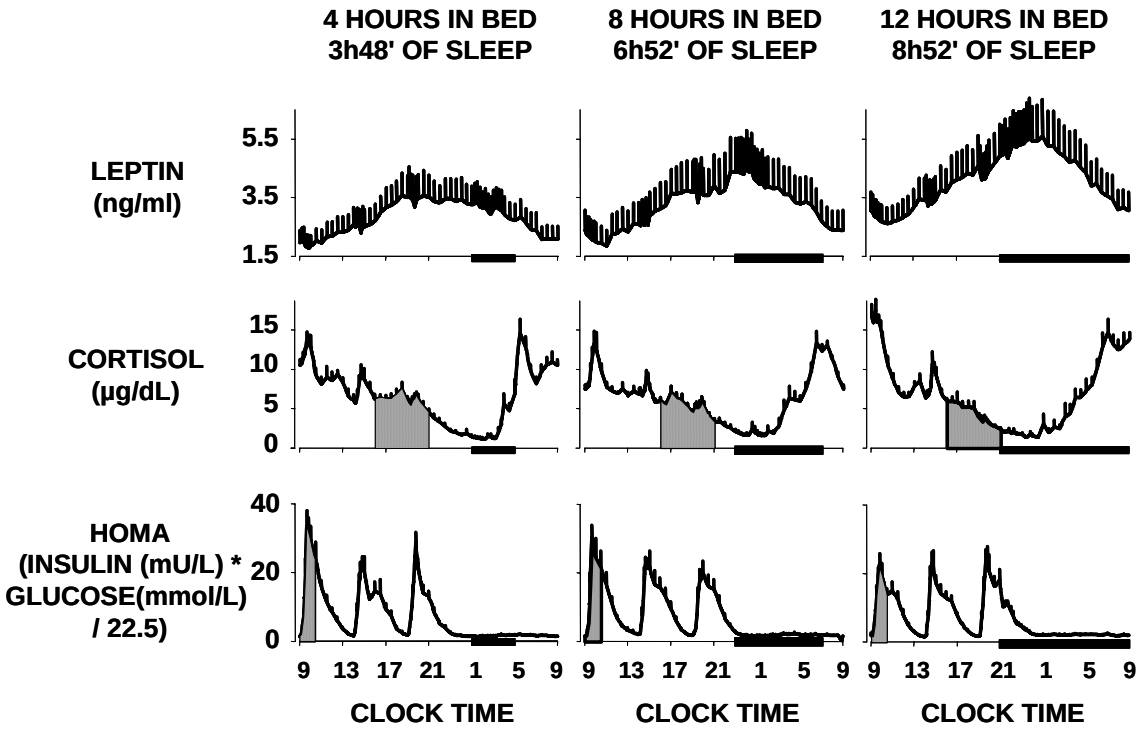

Spiegel et al, 2004 (19)
4h vs 10h
n=12
BMI constant
Taheri et al, 2004 (20)
5h vs 8h
n=1024
BMI adjustment
Chaput et al, 2007 (21)
5-6h vs level predicted
By BMI
n=740
Body fat adjustment
% Difference
30%
20%
10%
0%
-10%
-20%
Not Measured
Leptin
Ghrelin

Figure 5


4 HOURS IN BED
3h48' OF SLEEP
8 HOURS IN BED
6h52' OF SLEEP
12 HOURS IN BED
8h52' OF SLEEP
LEPTIN
(ng/ml)
5.5
3.5
1.5
CORTISOL
(µg/dL)
15
10
5
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HOMA
(INSULIN (mU/L) *
GLUCOSE(mmol/L)
/ 22.5)
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20
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9 13 17 21 1 5 9
CLOCK TIME

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Sleep Medicine 9 Suppl. 1 (2008) S23–S28

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Original article

Metabolic consequences of sleep and sleep loss

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Abstract

Reduced sleep duration and quality appear to be endemic in modern society. Curtailment of the bedtime period to minimum tolerability is thought to be efficient and harmless by many. It has been known for several decades that sleep is a major modulator of hormonal release, glucose regulation and cardiovascular function. In particular, slow wave sleep (SWS), thought to be the most restorative sleep stage, is associated with decreased heart rate, blood pressure, sympathetic nervous activity and cerebral glucose utilization, compared with wakefulness. During SWS, the anabolic growth hormone is released while the stress hormone cortisol is inhibited. In recent years, laboratory and epidemiologic evidence have converged to indicate that sleep loss may be a novel risk factor for obesity and type 2 diabetes. The increased risk of obesity is possibly linked to the effect of sleep loss on hormones that play a major role in the central control of appetite and energy expenditure, such as leptin and ghrelin. Reduced leptin and increased ghrelin levels correlate with increases in subjective hunger when individuals are sleep restricted rather than well rested. Given the evidence, sleep curtailment appears to be an important, yet modifiable, risk factor for the metabolic syndrome, diabetes and obesity. The marked decrease in average sleep duration in the last 50 years coinciding with the increased prevalence of obesity, together with the observed adverse effects of recurrent partial sleep deprivation on metabolism and hormonal processes, may have important implications for public health.

Keywords: Sleep deprivation; Glucose metabolism; Diabetes; Appetite regulation; Leptin; Ghrelin; Obesity

1. Sleep patterns in society

For a variety of reasons, either by lifestyle choice, imposed by work or family demands, or due to physical or psychological problems, chronic sleep deprivation is increasingly common in our hectic modern society [1,2]. Societal changes, such as an increase in television viewing and internet use, have impacted sleep patterns, leading to chronic sleep deprivation in a substantial proportion of the population [1]. Over the past 50 years, sleep duration in adults and adolescents has decreased by 1.5–2 hours per night, and more than 30% of Americans between the ages of 30 and 64 report sleeping less than 6 hours per night [3]. In addition to societal impact, the aging of the population in Western countries is associated with a decrease in average sleep duration as older adults obtain on average 2 hours less sleep per night than younger adults, a deficit that is independent of the increased incidence of age-related disorders which can impact sleep patterns [4,5]. Furthermore, the quality of sleep declines with age, with a major reduction in the duration of slow wave sleep (SWS) and increased sleep fragmentation [4].

2. Hormone release is modulated by sleep

SWS or deep sleep occurs during stages 3 and 4 of non-rapid eye movement (REM) sleep and is thought to be the most restorative of all sleep stages. Most slow wave activity occurs in the first two sleep cycles (approximately the first 3 hours of sleep), and the total amount of SWS per night is drastically reduced with age. Several important physiological activities only occur during the SWS, including a reduction in heart rate, blood pressure, sympathetic nervous activity and an increase in vagal tone [6]. SWS is also associated with a decrease in brain glucose metabolism [7]. Additionally, SWS exerts major modulatory effects on endocrine release. The release of the hormones of the hypothalamamic–pituitary–adrenocortical (HPA) system is increased [8], whereas the release of growth hormone (GH) and prolactin is increased. Both GH and cortisol have important roles in glucose metabolism. Laboratory studies have shown that the levels of these metabolic hormones are adversely affected by acute total sleep deprivation [9]. Studies in normal sleepers have shown that nocturnal GH release is reduced in individuals

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who are totally sleep deprived, but subsequently increases during daytime recovery sleep (with the reverse observed for cortisol release) [2].

An analysis of data from a series of studies was undertaken to determine the chronology of age-related changes in sleep duration and sleep quality in 149 healthy men, and whether sleep changes were associated with hormonal alterations [4]. The study found that the mean percentage of SWS decreased from 18.9% during early adulthood (age 16–25 years) to 3.4% during midlife (age 36–50 years), but remained unchanged from midlife to late life (age 71–83 years). Also, a significant decrease in sleep duration was observed across the age groups: each 10-year increment in age was associated with a 28-minute decrease in sleep duration ($P < 0.001$). The reductions in SWS observed with age were associated with a significant decline in GH secretion both from early to midlife ($P < 0.001$) and from midlife to late life ($P < 0.02$), and reductions in GH secretion were significantly associated with reductions in SWS independent of age ($P < 0.001$) [4].

Although the full clinical impact of chronic sleep deprivation on metabolic hormone release is yet to be determined, evidence indicates that dysfunction of glucose metabolism, obesity and increased diabetes risk are all likely outcomes [9].

3. Effect of sleep deprivation on carbohydrate metabolism and diabetes risk

Sleep appears to play an important role in the control of blood glucose levels, and recurrent partial sleep deprivation has been shown to have detrimental effects on carbohydrate metabolism and endocrine function [9,10]. A sleep debt study compared glucose metabolism in 11 young men undergoing periods of enforced partial sleep deprivation (4 hours sleep per night), sleep extension (12 hours sleep per night) and "normal" sleep as a baseline (8 hours sleep per night). During the sleep-restriction period, the individuals had significantly impaired glucose tolerance ($P < 0.04$; measured using the intravenous glucose tolerance test [IVGTT]), and significant reductions in their acute insulin response to glucose ($P = 0.05$) and in glucose effectiveness ($P < 0.0005$), compared with those observed when they were fully rested [10]. Insulin sensitivity was also reduced (5.41 versus 6.73×10^4/min/μU/mL), but this was not statistically significant [10]. The disposition index, a product of the acute insulin response to glucose and insulin sensitivity [11] and a marker of diabetic risk used in genetic studies [12], was significantly lower following sleep restriction than when the individuals were fully rested ($P = 0.0006$) [10].

Another study in young healthy adults showed that suppression of SWS without any reduction in total sleep time, correlated with decreased insulin sensitivity, reduced glucose tolerance and increased risk of type 2 diabetes, suggesting that a reduction in SWS (such as that seen in the elderly and in many obese individuals), independent of the overall duration of sleep, may be particularly important for normal glucose metabolism [13]. The mechanisms by which sleep deprivation impacts glucose tolerance are thought to be multifactorial, including decreased brain glucose utilization, alterations in the sympatho-vagal balance, increased evening cortisol and night-time GH levels, and proinflammatory processes [14].

The impact of short sleep duration on the risk of diabetes has been shown in several epidemiological studies, with a significant increase in incidence of diabetes in individuals who have difficulty in maintaining sleep or who experience chronic short sleep duration [15–17]. The largest of these, the prospective 10-year Nurses Health Study in 70,026 women [15], showed that individuals who slept 5 hours per night or less had a significantly higher risk of being diagnosed with diabetes (odds ratio [OR] 1.57, 95% CI: 1.28–1.92) compared with those who slept 8 hours per night, although this association was not significant after adjustment for obesity and other confounding factors (OR 1.18, 95% CI: 0.96–1.44). However, the increase in the risk of *symptomatic* diabetes with ⩽5 hours sleep per night versus 8 hours remained significant even after adjustment (OR 1.34, 95% CI: 1.04–1.72), suggesting that, although diabetes risk is increased by obesity (which appears to be more prevalent in short sleepers and, conversely, may result in poor sleep quality), insufficient sleep may be a risk factor for more severe diabetes [15].

Data from laboratory and epidemiological studies suggest that in addition to changes in glucose/carbohydrate metabolism, the relationship between sleep deprivation and diabetes risk may also involve upregulation of appetite and decreased energy expenditure, both of which can lead to obesity, itself a major risk factor for diabetes [14].

4. Sleep duration and appetite regulation

Food intake is controlled by the neuroendocrine system which is itself controlled by the central nervous system [18]. Long-term regulators of food intake include insulin and leptin, which are released in proportion to the amount of body fat. These hormones exert sustained inhibitory effects on food intake while increasing energy expenditure [18]. Ghrelin, on the other hand, is an appetite stimulating hormone released by cells in the stomach and the pancreas. In the non-pathological state, ghrelin levels rise rapidly before meals and fall equally rapidly after food intake (Figure 1). Both ghrelin and leptin are part of the orexin system, which integrates control of feeding, wakefulness and energy expenditure in the body, and they exert their influence on the central nervous system via receptors in the "appetite center" of the brain: the ventromedial and arcuate nuclei of the hypothalamus. Although the exact mechanisms are unclear, leptin and ghrelin are thought to act in parallel as opposing metabolic counterparts for body mass homeostasis [19].

Sleep duration plays an important role in the regulation of leptin and ghrelin levels in humans: several studies have shown that recurrent partial sleep deprivation and chronic short sleep are associated with a significant decrease in levels of leptin and increase levels of ghrelin (Figure 2A) [20–23]. In a randomized, cross-over study, 2 nights of short sleep

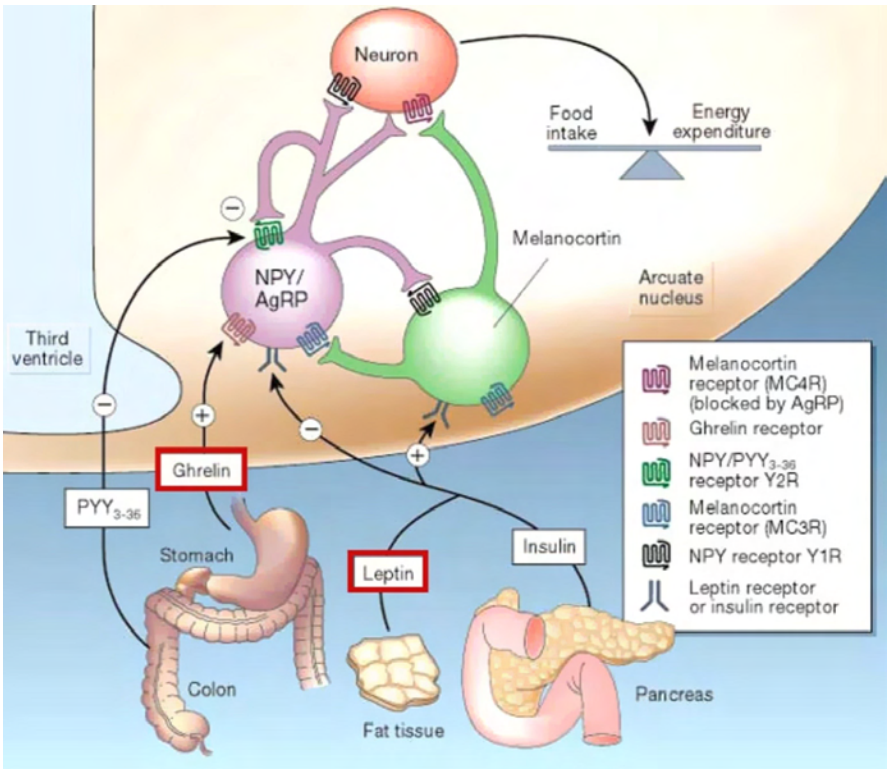

Fig. 1. Hormonal control of appetite and hunger [18]. NPY: neuropeptide Y; PYY: peptide YY, AgRP: agouti-related protein. Reprinted by permission from Macmillan Publishers Ltd: Nature, Schwartz MW et al. 2002 Aug 8;418(6898):595–7. Copyright © 2002.

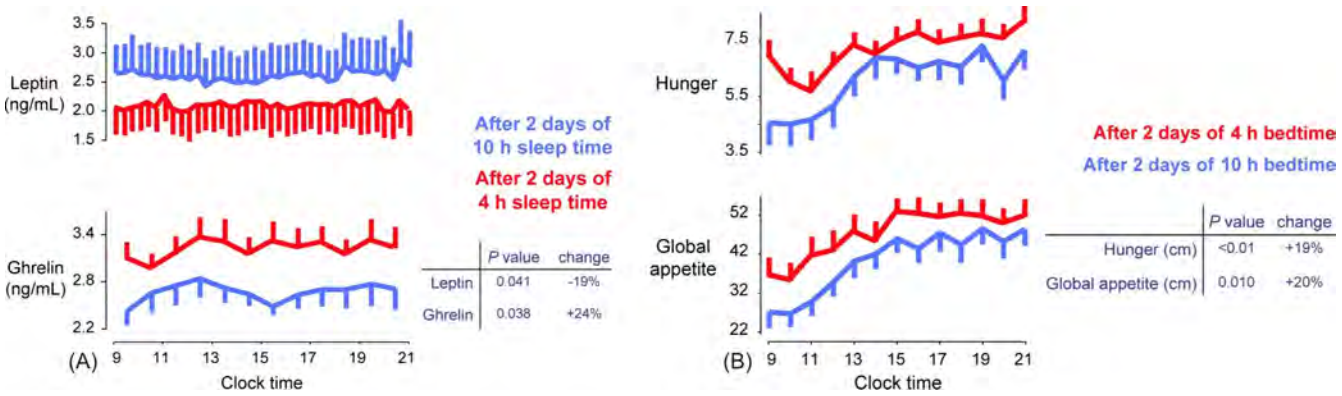

Fig. 2. The effect of sleep deprivation on (A) leptin and ghrelin levels and (B) hunger and global appetite ratings [21]. ANNALS OF INTERNAL MEDICINE. ONLINE by Spiegel K, Tasali E, Penev P, Van Cauter E. Copyright © 2004 by American College of Physicians – Journals. Reproduced with permission of American College of Physicians – Journals in the format Journal via Copyright Clearance Center.

(4 hours) were compared with 2 nights of long sleep (10 hours) on metabolic parameters. Results showed that a significant decrease in mean blood leptin levels ($P = 0.041$) occurred concomitantly with a significant increase in mean ghrelin levels ($P = 0.038$) after sleep restriction, compared with sleep extension, despite identical conditions of caloric intake [21]. Compared with sleep extension, sleep restriction was associated with significantly increased hunger ($P < 0.01$) and global appetite ($P = 0.01$). Importantly, the increased hunger and appetite reported, especially for carbohydrate-rich foods, correlated with the increased ghrelin:leptin ratio ($P = 0.014$; Figure 2B) [21].

In another study, 24-hour hormonal and glucose profiles were sampled at frequent intervals in 11 individuals studied after 6 days of 4 hours in bed (sleep restriction) and after 6 days of 12 hours in bed (sleep extension) while calorie intake and activity levels were carefully controlled. Mean and peak levels, and rhythm amplitude of leptin concentration over 24 hours were all decreased (–19%, –26% and –20%, respectively) during sleep restriction compared with sleep extension [20]. The 26% reduction in peak leptin levels observed during sleep restriction is similar to a mean 22% reduction reported in healthy volunteers after 3 days of dietary restriction (70% of energy requirements) [24].

Similar changes in leptin and/or ghrelin have been observed in two large epidemiological studies [22,23]. In a study of 1,024 volunteers from the Wisconsin Sleep Cohort, a significant reduction in leptin levels ($P = 0.01$) and elevation of ghrelin levels ($P = 0.008$) was observed with 5 hours versus 8 hours sleep duration [22]. Given that the leptin and ghrelin changes are likely to increase appetite, this could explain the increase in body mass index (BMI) observed with chronic short sleep duration [22]. In the second study of 740 male and female participants from the Quebec Family Study it was shown that short sleep duration (5–6 hours per night) was associated with significantly lower leptin levels than were predicted by body fat mass alone ($P < 0.01$) [23].

5. Sleep duration and obesity

Over the past 50 years, the prevalence of obesity has increased at a rapid rate and most experts agree that reductions in physical activity and changes in food marketing practices (i.e., portion size) do not fully explain this epidemic. During the same time frame, a corresponding decrease in self-reported sleep hours has been reported (Figure 3), suggesting that the two may be linked [2]. Indeed, a number of population-based studies involving more than 500,000 adults [22,23,25–38] and 28,000 children [39–45] have identified short sleep duration to be an important, yet modifiable, risk factor for obesity. Moreover, these findings have been confirmed in prospective longitudinal studies in both European and American adults [31,46,47] and children [42,44]. A recent systematic review of both cross-sectional and longitudinal studies [48] concluded that "short sleep duration appears independently associated with weight gain, particularly in young age groups".

The Quebec Family Study [23] was unique in also assessing adiposity and leptin levels and showed that both obesity and adiposity were reduced with 7–8 hours sleep compared with 5–6 hours. The adjusted OR for overweight/obesity (with 7–8 hours of sleep as reference) was 1.69 (95% CI: 1.15–2.39) for 5–6 hours of sleep and 1.38 (95% CI: 0.89–2.10) for 9–10 hours of sleep. Short sleep duration was also shown to be associated with reduced leptin levels after controlling for the degree of adiposity (as discussed above). The differences in obesity and adiposity between short sleepers and normal sleepers did not remain significant after adjustment for plasma leptin levels, implicating leptin as a potential mediator of the association between sleep duration and adiposity [23]. A recent meta-analysis of 30 cross-sectional studies investigated the relationship between sleep duration and obesity or BMI in adults and children (12 studies in children [n = 30,002] and 18 studies in adults [n = 604,509]) from around the world [49]. The risk of obesity was increased with short sleep duration in children (OR 1.89, 95% CI: 1.46–2.43; $P < 0.0001$) and in adults (OR 1.55, 95% CI: 1.43–1.68; $P < 0.0001$) [49]. The definition of short sleep duration varied among the studies, but was < 10 or $\leqslant 10$ hours per night for children and < 5 or $\leqslant 5$ hours average total sleep time per 24 hours for adults in the majority of studies included. Obesity was defined using national or international growth charts (BMI $\geqslant 30\ kg/m^2$ in adults). Studies varied in the degree of control for confounding factors such as age, gender, socioeconomic status, energy intake and expenditure, and comorbidity, particularly psychiatric disorders. As with other cross-sectional studies examining the relationship between sleep duration and obesity, the results of this meta-analysis, show an association but not causality between the two.

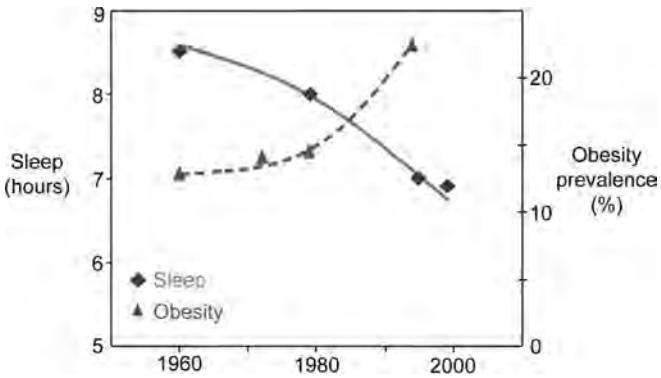

Fig. 3. Prevalence of obesity and self-reported sleep in the USA [2]. Reprinted with permission from *Medscape Neurology and Neurosurgery 2005. 7(1)*
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Although laboratory studies and prospective epidemiological studies suggest that short sleep duration may be a causal factor for obesity, the reverse direction of causality, i.e., that obesity can cause sleep disruption, is also possible, resulting in a vicious circle linking poor/short sleep and the risk of obesity. Further research is required to elucidate the mechanisms of the relationship.

6. Conclusion

Adequate sleep duration and quality are important for the normal functioning of daily metabolic and hormonal processes and appetite regulation. It is clear that chronic sleep deprivation has deleterious effects on carbohydrate metabolism and is associated with an increased risk of diabetes. Altered levels of hormones central to appetite regulation, such as leptin and ghrelin, occur in sleep-deprived individuals and, consistent with this neuroendocrine dysregulation of hunger and appetite, a large number of epidemiological studies have identified short sleep duration as a putative novel risk factor for weight gain and obesity. With the marked changes in sleep patterns that seem to have occurred in westernized countries over the last 50 years and an apparent reduction in average hours of sleep way beyond that predicted by aging of the population alone, it is probable that an increasing proportion of people suffer from chronic sleep deprivation. This has important implications for individual physical and psychological well being and serious consequences for society as a whole. Avoiding the build up of a chronic sleep debt through awareness, education and effective management of sleep disorders may be important

to limit the rise in cardiometabolic dysfunction, diabetes and obesity that has occurred over recent years.

Acknowledgements

Work partly supported by NIH grants PO1 AG-11412, RO1 HL-075079 and P60 DK-20595 and by grant W81XWH-07–2–0071 of the US Department of Defence. We thank Matt Weitz, from Wolters Kluwer Health, who provided medical writing support on behalf of sanofi-aventis.

Disclosures

None.

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